Aromatic Fluoroalkoxylation via Direct Aromatic Nucleophilic Substitution[1]

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The reaction of activated aryl and heteroaryl halides with fluorinated alkoxide anions is described. In all cases, substitution of the halogen by a fluoroalkoxy group was observed. The effect of solvent, time, temperature, the activating group, leaving group, and the nucleophile on this reaction is also discussed.

Considerable time and attention have been and continue to be directed toward the syntheses of fluorinated organic materials.[2] In the case of fluoroalkoxy aromatics, the majority of the previously reported synthetic procedures involve the reaction of an electrophilic haloalkyl fluoride, fluoroalkene, or a fluoroalkyl sulfonate with a nucleophilic phenol derivative.[2-4] While these procedures provide access to the fluoroalkoxy aromatic system, they do not offer the convenience and simplicity of methods reported by Shaw[5] and Kornblum[6] for the direct introduction of the corresponding alkoxy groups. However, we have recently reported[7] that good yields of (2,2,2-trifluoroethoxy)-benzenes can be obtained by a direct aromatic nucleophilic substitution reaction between sodium 2,2,2-trifluoroethoxide and cyano-substituted chlorobenzenes in HMPA at temperatures of 90–150 °C. In an effort to define the scope and limitation of this direct aromatic nucleophilic fluoroalkoxylation reaction, we report here our studies on the effect of solvent, time, substrate, leaving group, and nucleophile.

Results and Discussion

Effect of Solvent and Time on Trifluoroethoxylation. While Shaw's[5] and Kornblum's[6] reports on direct alkoxylation of aromatic systems and our initial studies[7] on direct fluoroalkoxylation employ HMPA as the solvent, any dipolar, aprotic solvent that is able to provide the necessary polarity and temperature control should, in principle, promote the reaction. In the case of fluoroalkoxylation, the use of an alternate solvent could be particularly advantageous in order to avoid a temperature-dependent reaction of HMPA with an activated aryl halide, which, as we have recently reported,[8] occurs at temperatures around 150 °C.

The reaction of 4-chlorobenzonitrile and sodium 2,2,2-trifluoroethoxide has been investigated in HMPA, DMF, 1-methyl-2-pyrrolidinone and Me_2SO. While the recrystallized yields of the product in each case are essentially the same, DMF should generally be considered the solvent of choice. In addition, the percent conversion of 4-chlorobenzonitrile to 4-(2,2,2-trifluoroethoxy)benzonitrile in HMPA and is DMF is comparable (93% and 85%, respectively) after 2 h and shows no change in either case after 8 h.

Effect of Substrate on Trifluoroethoxylation. As indicated in Tables I and II, a variety of substituted chlorobenzenes and chloroheterocycles were investigated as substrates toward reaction with sodium 2,2,2-trifluoroethoxide. As expected, the cyano and nitro groups are very effective in activating the benzene ring toward reaction with trifluoroethoxide ion, including substrates in which the activating group is substituted meta to the leaving group (entry 2, Table I) as well as ones that also contain an electron-releasing group (entry 4, Table I). When two activating groups are present (entry 5, Table I), the reaction will occur at less than 100 °C. Interestingly, the trifluoromethyl, phenylcarbonyl, and phenylsulfonyl groups are sufficiently activating so as to be synthetically useful (entries 10–13, Table I). In the case of the bis(4-chlorophenyl) sulfone, one or both of the chlorines can be displaced, depending on the amount of sodium 2,2,2-trifluoroethoxide present. Chloro, aldehydo, or amido functionalities in a chlorobenzene provide either no reaction or only traces of product (entries 6, 14, and 15, Table I, respectively). The reaction of chloroheterocyclic compounds with trifluoroethoxide ion should be particularly useful synthetically as indicated by the examples shown in Table II, which include both unsubstituted and electron-releasing-group substituted substrates.

Effect of Leaving Group on Trifluoroethoxylation. In order to further define the reaction of trifluoroethoxide ion with aromatic substrates, the effect of various leaving groups in an ortho-substituted nitrobenzene has been studied and is reported in Table III. The observed order of reactivity (o-NO_2, m-NO_2 slightly > o-F, o-Cl > o-Br > o-I) is typical of a two-step S_NAr reaction in which the first step is rate determining. That is, fluoro is generally the poorest leaving group among the halogens when the second step of the S_NAr mechanism is rate determining or when a benzyne mechanism is operative.[9]

While the nitro group is generally a good leaving group in alkoxide ion promoted aromatic substitutions,[6,10] its ability to be displaced by a trifluoroalkoxide ion is particularly interesting and provides a convenient, alternate synthetic entry to fluoroalkoxy aromatics.

Effect of Various Fluoroalkoxide Ions in Aromatic Fluoroalkoxylation. The synthetic utility of several fluoroalkoxide ions other than the trifluoroethoxide ion has been investigated, and the results are reported in Table IV. As indicated, fluoroalkoxide ions of general structure $OCHRC_xF_y$ where R = H or CH_3, x = 1 or 2, and y = 3 or 4 promote synthetically useful reactions to provide the

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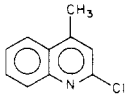
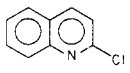
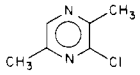
Table I. Reaction of Activated Benzenes with $NaOCH_2CF_3$ in HMPA at 150 °C[a]

entry	product	benzene X	benzene Y	benzene Z	mp or bp, °C	yield %
1	1a	2-CN	H	Cl	73-74	95
2	1b	3-CN	H	Cl	49-50	79
3	1c	4-CN	H	Cl	60-61	91
4	1d	2-CN	3-CH_3	Cl	88-92	97
5	1e	2-CN	4-NO_2	Cl	94-96	98[b]
6	1f	2-Cl	H	H		trace
7	1g	2-NO_2	H	Cl	114 (3 mm)	95[c]
8	1h	3-NO_2	H	NO_2	57-59	79
9	1i	4-NO_2	H	Cl	75-78	88
10	1j	4-CF_3	H	Cl	83-85 (40 mm)	32
11	1k	4-(4-ClPhSO_2)	H	Cl	125-126	60[d]
12	1l	4-(4-ClPhSO_2)	H	Cl	150-151	69[e]
13	1m	4-COPh	H	Cl	61-63	54
14	1n	2-CHO	H	Cl		
15	1o	4-CON(CH_3)$_2$	H	Cl		trace[f]

[a] Reaction time was 15 h unless otherwise noted. [b] Reaction was run at 90 °C. [c] Reaction time was 2 h. [d] Reaction was run at 140 °C for 12 h with 1 equiv of $NaOCH_2CF_3$ to give the monosubstituted product. [e] Reaction was run at 150 °C for 15 h with 2 equiv of $NaOCH_2CF_3$ to give the disubstituted product. [f] Reaction time was 12 h. All the products presented in Table I were purified by distillation or recrystallization and were found to be greater than 90% pure as determined by thin-layer chromatography on silica gel 7GF with chloroform as the eluant (R_f values between 0.2 and 0.8). Entries 11 and 12 were the only exceptions. Entry 11 (monosubstituted) was contaminated with some 12 (disubstituted) and entry 12 was contaminated with some 11. In each case the minor component amounted to 10-15% of the product.

Table II. Reaction of Chloroheterocyclics with $NaOCH_2CF_3$ in HMPA at 150 °C[a]

product	substrate	mp or bp, °C	yield, %
2a		68-71 (0.3 mm)	54
2b		58-59	51
2c		30-35 (0.5 mm)	54
2d		33-36 (0.2 mm)	43

[a] Reaction time was 15 h in all cases. All the products presented in this table were purified by distillation or recrystallization and were found to be greater than 90% pure as determined by thin-layer chromatography on silica gel 7GF with chloroform as the eluant (R_f values between 0.2 and 0.8).

Table III. Reaction of Substituted Nitrobenzenes (X-Ph-NO_2) with $NaOCH_2CF_3$ in HMPA at 150 °C[a]

X	conversion,[b] %	X	conversion,[b] %
o-NO_2	98	o-Cl	95
m-NO_2	98	o-Br	34
o-F	93	o-I	8

[a] Reaction time was 2 h in all cases. [b] Calculated from NMR spectrum of reaction product.

corresponding fluoroalkoxylated product. On the other hand, tertiary fluoroalkoxide ions (e.g., entry c, Table IV) or fluoroalkoxide ions containing more than four fluorines (entries e and f, Table IV) promote little, if any, direct aromatic fluoroalkoxylation.

In conclusion, this new procedure for direct fluoroalkoxylation provides a clean, simple, and efficient method for obtaining a wide variety of substituted aryl and heteroaryl fluoroalkoxylated substances. The only significant limitations on this transformation seems to be the degree of fluorination on the alkoxide nucleophile.

Table IV. Reaction of 4-Chlorobenzonitrile with Various Sodium Fluoroalkoxides ($Na^+ {}^-OR_F$) in HMPA

entry	product	R_F of ^-OR_F	reaction temp, °C	reaction time, h	yield, %
a	3b	CH_2CF_3	150	15	91
b		$CH(CH_3)CF_3$	150	6	72
c		$C(CH_3)_2CF_3$	150	32	
d	3d	$CH_2CF_2CF_2H$	200	6	40
e		$CH(CF_3)CF_3$	135	24	
f		$CH_2(CF_2)_2CF_3$	150	24	

Experimental Section[11]

The following procedure is typical of the experimental conditions used for reaction of activated aromatic or heteroaromatic compounds with fluorinated alkoxide anions.

***o*-(2,2,2-Trifluoroethoxy)benzonitrile (1a).** To a mixture of 2.6 g (0.055 mol) of hexane washed sodium hydride in 50 mL of HMPA (dried over 4-Å molecular sieves) is added 10.0 g (0.10 mol) of 2,2,2-trifluoroethanol. The mixture is stirred for 20 min, and 6.9 g (0.05 mol) of 2-chlorobenzonitrile is added in one portion. The resulting mixture is heated at 90–150 °C overnight, and after being cooled to room temperature, it is poured into 100 mL of 5% aqueous hydrochloric acid. If the product does not crystallize immediately, the mixture is extracted with ether (3 × 70 mL) and the combined ether extracts are washed with additional aqueous hydrochloric acid (2 × 50 mL). After drying the ether phase over

(11) Infrared spectra were recorded on a Perkin-Elmer Model 457 infrared spectrophotometer or on a Nicolet MX-S FT–IR spectrometer. Samples were run as thin films, Nujol mulls, or $CHCl_3$ or CCl_4 solutions. NMR spectra were obtained in CCl_4, $CDCl_3$, or Me_2SO-d_6 solutions [$(CH_3)_4Si$ as internal standard] at 60 Mz with a Varian EM-360A spectrometer. All boiling points and melting points are uncorrected, and melting points were recorded on a Fisher-Johns melting-point apparatus. All starting materials used in this work were purchased from either Aldrich Chemical Co., Milwaukee, WI, or PCR Research Chemicals, Inc., Gainesville, FL. Combustion analyses were carried out by Robertson Laboratory, Inc., of Florham Park, NJ.

anhydrous magnesium sulfate and concentrating it in vacuo, the *o*-(2,2,2-trifluoroethoxy)benzonitrile is obtained as a tan solid (95% crude yield). The product can be recrystallized from a 4 to 1 water/2-propanol mixture if desired: NMR ($CDCl_3$) δ 4.53 (q, J = 8 Hz, 2 H) and 6.87–7.83 (m, 4 H); IR ($CHCl_3$) 3080, 2230, 1600, 1580, 1490, 1450, 1250, 1110, and 1060 cm^{-1}; mass spectrum, m/e 201 (M^+).

The spectral data for compounds **1b**, **1d**, and **1e** have been previously reported.[7]

***p*-(2,2,2-Trifluoroethoxy)benzonitrile (1c)**: NMR ($CDCl_3$) δ 4.50 (q, J = 8 Hz, 2 H), 7.08 (d, J = 8 Hz, 2 H) and 7.70 (d, J = 8 Hz, 2 H); IR ($CHCl_3$) 3080, 2220, 1600, 1500, 1280, 1240, 1170, 1070, 970, and 830 cm^{-1}; mass spectrum, m/e 201 (M^+).

Anal. Calcd for $C_9H_6NOF_3$: C, 53.73; H, 3.01; N, 6.96; F, 28.33. Found: C, 53.90; H, 2.96; N, 6.99; F, 28.39.

***o*-(2,2,2-Trifluoroethoxy)nitrobenzene (1g)**: NMR ($CDCl_3$) δ 4.58 (q, J = 8 Hz, 2 H) and 7.00–8.22 (m, 4 H); IR (thin film) 1615, 1535, 1360, 1175, 870, 780, 750, and 695 cm^{-1}; mass spectrum, m/e 221 (M^+).

***m*-(2,2,2-Trifluoroethoxy)nitrobenzene (1h)**: NMR ($CDCl_3$) δ 4.50 (q, J = 8 Hz, 2 H) and 7.20–8.13 (m, 4 H); IR (Nujol) 1600, 1535, 1360, 1170, 865, 820, 750, and 660 cm^{-1}; mass spectrum, m/e 221 (M^+).

***p*-(2,2,2-Trifluoroethoxy)nitrobenzene (1i)**: NMR ($CDCl_3$) δ 4.50 (q, J = 8 Hz, 2 H), 7.15 (d, J = 10 Hz, 2 H), and 8.27 (d, J = 10 Hz, 2 H); IR (Nujol) 1600, 1500, 1350, 1170, 870, 850, and 750 cm^{-1}; mass spectrum, m/e 221 (M^+).

***p*-(2,2,2-Trifluoroethoxy)benzotrifluoride (1j)**: NMR ($CDCl_3$) δ 4.40 (q, J = 8 Hz, 2 H), 7.03 (d, J = 8 Hz, 2 H), and 7.62 (d, J = 8 Hz, 2 H); IR (thin film) 1600, 1530, 1350, 1170, 870, 840, and 682 cm^{-1}; mass spectrum, m/e 244 (M^+).

4-(2,2,2-Trifluoroethoxy)phenyl 4-chlorophenyl sulfone (1k): NMR ($CDCl_3$) δ 4.40 (q, J = 8 Hz, 2 H), 7.08 (d, J = 8 Hz, 2 H), 7.50 (d, J = 8 Hz, 2 H), 7.90 (d, J = 8 Hz, 2 H), and 7.95 (d, J = 8 Hz, 2 H); IR (Nujol) 1600, 1300, 1170, 865, 850, and 770 cm^{-1}; mass spectrum , m/e 350 (M^+).

Bis[*p*-(2,2,2-Trifluoroethoxy)phenyl] sulfone (1l): (NMR ($CDCl_3$) δ 4.40 (q, J = 8 Hz, 4 H), 7.08 (d, J = 10 Hz, 4 H), and 7.95 (d, J = 10 Hz, 4 H); IR (Nujol) 1600, 1330, 1290, 1250, 1170, 870, and 845 cm^{-1}; mass spectrum, m/e 414 (M^+).

***p*-(2,2,2-Trifluoroethoxy)benzophenone (1m)**: NMR ($CDCl_3$) δ 4.47 (q, J = 8 Hz, 2 H), 7.08 (d, J = 8 Hz, 2 H), and 7.42–8.08 (m, 7 H); IR (Nujol) 1650, 1610, 1290, 1250, 1170, 850, 740, and 700 cm^{-1}; mass spectrum, m/e 280 (M^+).

4-Methyl-2-(2,2,2-trifluoroethoxy)quinoline (2a): NMR ($CDCl_3$) δ 2.32 (s, 3 H), 4.88 (q, J = 8 Hz, 2 H), 6.60 (s, 1 H), and 7.08–7.90 (m, 4 H); IR (thin film) 1620, 1590, 1280, 1170, 860, 760, and 700 cm^{-1}; mass spectrum, m/e 241 (M^+).

2-(2,2,2-Trifluoroethoxy)quinoline (2b): NMR ($CDCl_3$) δ 4.91 (q, J = 8 Hz, 2 H), 6.95 (d, J = 8 Hz, 1 H), 7.18–7.88 (m, 4 H), and 8.10 (d, J = 8 Hz, 1 H); IR (Nujol) 1615, 1270, 1170, 830, 760, 750, and 660 cm^{-1}; mass spectrum, m/e 227 (M^+).

Anal. Calcd for $C_{11}H_8NOF_3$: C, 58.15; H, 3.56; N, 6.17; F, 25.09. Found: C, 58.36; H, 3.51; N, 6.26; F, 24.79.

2,5-Dimethyl-3-(2,2,2-trifluoroethoxy)pyrazine (2c): NMR ($CDCl_3$) δ 2.40 (s, 3 H), 2.48 (s, 3 H), 4.80 (q, J = 8 Hz, 2 H), and 7.98 (s, 1 H); IR (thin film) 1590, 1470, 1380, 1275, 1170, 760, and 660 cm^{-1}; mass spectrum, m/e 206 (M^+).

2-(2,2,2-Trifluoroethoxy)pyrimidine (2d): NMR ($CDCl_3$) δ 4.90 (q, J = 8 Hz, 2 H), 7.17 (t, J = 5 Hz, 1 H), and 8.75 (d, J = 5 Hz, 2 H); IR (thin film) 1580, 1430 1270, 1160, 965, and 810 cm^{-1}; mass spectrum, m/e 178 (M^+).

Anal. Calcd for $C_6H_5N_2OF_3$: C, 40.45; H, 2.84; N, 15.73; F, 32.00. Found: C, 40.72; H, 2.92; N, 15.84; F, 32.25.

***p*-(1,1,1-Trifluoroisopropoxy)benzonitrile (3b)**: NMR ($CDCl_3$) δ 1.54 (d, J = 6 Hz, 3 H), 4.87 (hept, J = 6 Hz, 1 H), 7.10 (d, J = 10 Hz, 2 H), and 7.55 (d, J = 10 Hz, 2 H), IR (neat) 2200, 1600, 1510, 1400, 1280, 1250, 1160, 1180, 1090, 1020, and 840 cm^{-1}, mass spectrum, m/e 215 (M^+).

***p*-(2,2,3,3-Tetrafluoropropoxy)benzonitrile (3d)**: NMR ($CDCl_3$) δ 4.48 (t, J = 12 Hz, 2 H), 6.12 (t of t, J = 4 Hz, J = 54 Hz, 1 H), 7.10 (d, J = 8 Hz, 2 H), and 7.78 (d, J = 8 Hz, 2 H); IR (Nujol) 2240, 1610, 1370, 1270, 1180, 1100, 850, 840, and 735 cm^{-1}; mass spectrum, m/e 233 (M^+).

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Registry No. **1a**, 56935-77-4; **1b**, 84328-66-5; **1c**, 56935-76-3; **1d**, 84328-67-6; **1e**, 84328-69-8; **1g**, 87014-28-6; **1h**, 87014-29-7; **1i**, 62149-35-3; **1j**, 87014-30-0; **1k**, 87014-31-1; **1l**, 87014-32-2; **1m**, 87014-33-3; **2a**, 87014-34-4; **2b**, 87014-35-5; **2c**, 87014-36-6; **2d**, 87014-37-7; **3b**, 87014-38-8; **3d**, 87014-39-9; $NaOCH_2CF_3$, 420-87-1; $HOCH_2CF_3$, 75-89-8; $NaOCH(CH_3)CF_3$, 87014-40-2; $NaOC(CH_3)_2CF_3$, 87014-41-3; $NaOCH_2CF_2CF_2H$, 41578-54-5; $NaOCH(CF_3)CF_3$, 6919-74-0; $NaOCH_2(CF_2)CF_3$, 812-42-0; 2-chlorobenzonitrile, 873-32-5; 3-chlorobenzonitrile, 766-84-7; 4-chlorobenzonitrile, 623-03-0; 2-chloro-6-methylbenzonitrile, 6575-09-3; 2-chloro-5-nitrobenzonitrile, 16588-02-6; chlorobenzene, 108-90-7; 2-nitrochlorobenzene, 88-73-3; 1,3-dinitrobenzene, 99-65-0; 4-nitrochlorobenzene, 100-00-5; 4-(trifluoromethyl)chlorobenzene, 98-56-6; bis(4-chlorophenyl) sulfone, 80-07-9; 4-benzoylchlorobenzene, 134-85-0; 2-chlorobenzaldehyde, 89-98-5; 4-chloro-*N*,*N*-dimethylbenzamide, 14062-80-7; 2-chloro-4-methylquinoline, 634-47-9; 2-chloroquinoline, 612-62-4; 3-chloro-2,5-dimethylpyrazine, 95-89-6; 2-chloropyrimidine, 1722-12-9; 1,2-dinitrobenzene, 528-29-0; 2-fluoronitrobenzene, 1493-27-2; 2-bromonitrobenzene, 577-19-5; 2-iodonitrobenzene, 609-73-4.